Current perspectives

Stenting and abciximab in primary angioplasty: a review of current status

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Improvement of stent deployment techniques and advances in antiplatelet therapy have shown that stenting in the setting of ST-elevation myocardial infarction (STEMI) is safe and effective. Randomized trials have found that as compared to balloon angioplasty, coronary stenting does not reduce mortality and reinfarction, despite the reduction in target vessel revascularization. Furthermore, these benefits seem to be reduced when applied to unselected patients with STEMI. Direct stenting represents an attractive strategy with potential benefits in terms of myocardial perfusion. Future randomized trials are needed to evaluate if this strategy is associated with a significant impact on outcome, and to provide cost-benefit analysis of an unrestricted use of drug-eluting stent in this high-risk subset of patients.

Data from randomized trials have shown that the additional use of abciximab reduces mortality in primary angioplasty. Since the feasibility of long-distance transportation has been shown in several randomized trials, early pharmacological pretreatment may confer further advantages by early recanalization and shorter ischemic time, particularly in high-risk patients. Further large randomized trials are needed to clarify the potential role of small molecules in primary angioplasty for STEMI.

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For several years, stenting has been avoided in the setting of ST-elevation myocardial infarction (STEMI), because the implantation of a metallic device, within a thrombotic environment, such as that of a plaque disruption resulting in myocardial infarction, would be likely to precipitate stent thrombosis with resultant vessel occlusion. Vigorous anticoagulation, necessary to avoid stent thrombosis, exposed the patient to the risk of bleeding and vascular complications[1]. All these considerations have led most investigators to restrict stenting in STEMI to bail-out situations. However, improvement of stent deployment techniques and advances in antiplatelet therapy[2-5] have shown that stenting in the setting of STEMI is safe and effective[6-17].

Stenting in primary angioplasty

Results from randomized trials. As shown by data on long-term follow-up (2 years) from our randomized trial, stenting is a safe and cost-effective strategy for STEMI[6,7]. These findings have been confirmed by other randomized trials[8-17]. Grines et al.[11] randomized, in the stent PAMI trial, 452 patients to a heparin-coated stent and 448 to balloon angioplasty. They found that the better outcome, conferred by stent, was mainly accounted for a reduction in target vessel revascularization (TVR) at 12-month follow-up, as compared with balloon angioplasty alone. Some concerns came from the higher rate of mortality found in the stent group (5.8 vs 3.1%, p = NS). These results may be partially explained by the different levels of expertise in primary angioplasty at some of 65 participating centers that took part in the trial. This hypothesis is indirectly supported by the lower mortality rate (1.7%) observed in the PAMI pilot trial[17], where the enrolment was limited to 9 high-volume centers with experienced operators.

A recent meta-analysis reported data involving a total of 4120 patients randomized to stent (n = 2050) or balloon angioplasty (n = 2070) in 9 trials[18]. Patients in cardiogenic shock were included in FRESCO[8], GRAMI[9], PASTA[10], and PSAAMI[12], but were generally excluded in other trials, whereas CADILLAC[16] was the only trial that examined the comparative efficacy of

these two treatments alone and in combination with abciximab. As shown in figure 1, primary stenting reduced significantly the composite incidence of all adverse cardiac events, mainly due to a reduction in the need for TVR (9.2 vs 18.7%, odds ratio [OR] 0.43, 95% confidence interval [CI] 0.36-0.52, p < 0.001), without any statistically significant difference in mortality (3.7 vs 3.6%, OR 1.04, 95% CI 0.75-1.44, p = NS), and reinfarction (2.1 vs 2.9%, OR 0.71, 95% CI 0.47-1.08, p = 0.13).

Limitations of current randomized trials. Despite the demonstrated superiority of stenting in comparison with balloon angioplasty in patients with STEMI, stenting has not determined a reduction in reinfarction and death. Therefore, caution should be taken in extending these data to the "real world", because of the selection bias affecting these data.

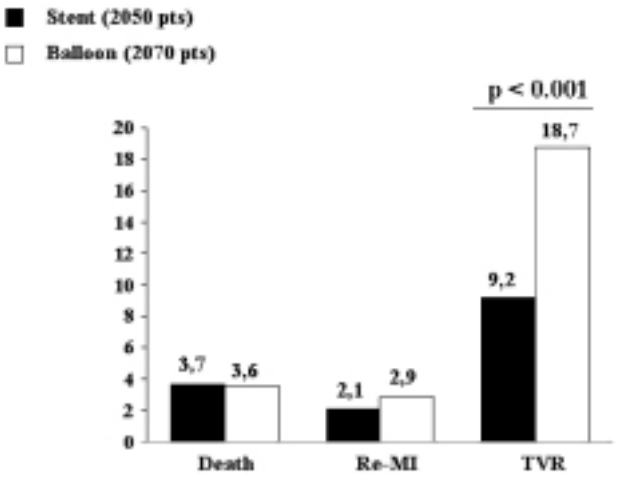

Figure 1. *Bar graphs show a pooled data analysis of the 6-12-month clinical outcome of patients with ST-elevation myocardial infarction (MI) randomized to balloon angioplasty or stenting. Primary stenting has been shown to be superior to balloon angioplasty, and this is mainly due to a significant reduction in restenosis after stenting, when compared to angioplasty. TVR = target vessel revascularization.*

Several potential factors for selection bias could have affected the results of these trials:

a) *role of randomization strategies.* According to the time of randomization, four major randomization strategies may be identified: 1) before the initial angiography; 2) before passing the guidewire across the occlusion; 3) after crossing the lesion with the guidewire or initial balloon inflation; and 4) after optimal balloon angioplasty.

In none of the trials, randomization was done before the initial angiography (Table I)[6,8-12,14,16]. Currently available data have mainly been obtained from highly selected patients. In fact, the knowledge of coronary anatomy before randomization may have excluded many patients who were considered non-suitable for stenting and those with unstable hemodynamic conditions. In fact, in our previous report[6], patients excluded from the trial had a significantly worst in-hospital outcome in comparison with those included in the study;

b) *actual-treatment analysis.* Most of data available from randomized trials, and from meta-analysis studies, come from intention-to-treat analysis, whereas a variable percentage of crossover, according to the randomization strategy, ranging from 0% in the FRESCO trial[8] to 35% in the STENTIM-2 trial[14], was observed;

c) *small, low-volume centers.* The results from many randomized trials were obtained from experienced centers. This makes these data not easily achievable in the community setting, as suggested by the results of large national registries[19]. This issue has been addressed by the GUSTO IIb trial[20] by testing the effects of angioplasty when performed in low-volume centers on a low-risk population. In this trial, in fact, a less favorable outcome was observed in comparison with other trials;

d) *angiographic follow-up.* As shown by the Benestent II trial[21], patients with angiographic follow-up have a significantly higher rate of TVR in comparison with those without planned angiographic follow-up. This may have partially contributed to the benefits observed

Table I. Characteristics according to the randomization strategy.

	No. patients	Ischemic time (hours)	Vessel diameter (mm)	Stent type	Crossover (%)	
					Stent	Balloon
Group 1	2517					
CADILLAC[16]	2082	12	2.5	MultiLink (Duet)	1	18
STENTIM-2[14]	211	12	3.0	Witkor-GX	3	36
PASTA[10]	136	12	2.5	Palmaz-Schatz	1	10
PSAAMI[12]	88	6	3.0	Tensum III	2	27
Group 2	1231					
Zwolle[6]	227	6	3.0	Palmaz-Schatz	2	13
GRAMI[9]	104	24	2.5	Gianturco-Rubin II	0	25
Stent PAMI[11]*	900	12	3.0	Palmaz-Schatz	2	15
Group 3	150					
FRESCO[8]	150	6	2.5	Gianturco-Rubin	0	0

* heparin-coated stent.

with coronary stenting in almost all previous randomized trial.

Therefore, in order to overcome the above-mentioned limitations, we have conducted a prospective randomized trial to investigate the actual role of routine stenting as compared to balloon angioplasty, in a large cohort of unselected, consecutive patients with STEMI, enrolled before the initial angiography[22].

No difference was observed in terms of procedural success and distal embolization (Table II). In consistence with our data, Kastrati et al.[23] found no difference in myocardial salvage between stent and balloon angioplasty for STEMI.

At 1-year follow-up, stenting was not associated with benefits in terms of mortality and reinfarction. Despite the significant reduction in restenosis with coronary stenting at angiographic follow-up (34.3 vs 42.4%, p = 0.037), no difference in TVR was observed.

These data have been confirmed even in the analysis conducted according to the final treatment (Table II) and in those patients who did not undergo routine angiographic follow-up (Table III).

Table III. Clinical outcome at 30-day and 1-year follow-up (according to the intention-to-treat analysis) in patients who did not undergo routine angiographic follow-up.

	Stent (n=479)	Balloon (n=442)	p
30 days			
Death	23 (4.8%)	31 (7.0%)	NS
Re-MI	14 (2.9%)	14 (3.2%)	NS
Death and/or re-MI	32 (6.7%)	41 (9.3%)	NS
SAT	8 (1.7%)	3 (0.7%)	NS
TVR	9 (1.9%)	5 (1.1%)	NS
MACE	44 (9.2%)	62 (14.0%)	0.021
1 year			
Death	44 (9.2%)	39 (8.8%)	NS
Re-MI	24 (5.0%)	21 (4.8%)	NS
Death and/or re-MI	59 (12.3%)	54 (12.2%)	NS
SAT	10 (2.1%)	3 (0.7%)	NS
TVR	18 (3.8%)	13 (2.9%)	NS
MACE	90 (18.8%)	90 (20.4%)	NS

MACE = major adverse cardiac events (death, reinfarction, and/or TVR); MI = myocardial infarction; SAT = subacute thrombosis; TVR = target vessel revascularization.

Direct stenting strategy in primary angioplasty. Recently, the availability of premounted stents has let direct stenting implantation become, when technically feasible, the best preferred strategy, determining a significant reduction of costs, radiation exposure[24], and a better postprocedural flow in comparison with conventional stenting implantation[25]. In fact, in animal models direct stenting limits the extent of endothelial ablation and reduces neointimal hyperplasia[26]. Thus, direct stenting strategy seems very attractive in the infarct-related artery, where distal microembolization is a very common complication[27].

Loubeyre et al.[28] have recently reported their single-center experience in 206 patients randomized to direct stenting or conventional stenting. The cumulative angiographic incidence of slow-flow, no-reflow or distal embolization occurred in 12 patients (11.7%) in the direct stenting group and in 28 patients (26.9%) in the conventional stent group (p = 0.01). Conventional stenting was associated with a significantly higher incidence of no ST-segment resolution. This study has definitively demonstrated the feasibility of direct stenting in patients with STEMI. However, it should be remarked that direct stenting is applicable to a relatively

Table II. Clinical outcome at 30-day and 1-year follow-up according to the intention-to-treat and actual-treatment analyses.

	Intention-to-treat				Actual-treatment			
	Stent (n=849)	Balloon (n=834)	RR (95% CI)	p	Stent (n=890)	Balloon (n=658)	RR (95% CI)	p
30 days								
Death	4.2%	4.8%	0.86 (0.54-1.35)	NS	3.8%	3.8%	1.00 (0.59-1.7)	NS
Re-MI	5.9%	4.4%	1.37 (0.89-2.13)	NS	5.5%	3.2%	1.77 (1.05-2.98)	< 0.05
Death and/or re-MI	9.2%	8.5%	1.09 (0.78-1.52)	NS	8.2%	6.8%	1.22 (0.83-1.79)	NS
SAT	3.4%	2.2%	1.6 (0.88-2.91)	NS	3.8%	2.0%	1.97 (1.03-3.76)	< 0.05
TVR	9.1%	8.4%	1.09 (0.78-1.53)	NS	6.1%	6.4%	0.95 (0.62-1.44)	NS
MACE	13%	13.4%	0.96 (0.72-1.27)	NS	9.9%	10.0%	0.98 (0.70-1.38)	NS
1 year								
Death	7.1%	6.6%	1.12 (0.76-1.66)	NS	6.0%	5.9%	1.00 (0.65-1.52)	NS
Re-MI	8.4%	6.8%	1.33 (0.9-1.96)	NS	8.7%	5.0%	1.7 (1.07-2.7)	< 0.01
Death and/or re-MI	14.0%	12.4%	1.21 (0.91-1.62)	NS	13.0%	10.2%	1.34 (0.96-1.87)	NS
SAT	4.5%	3.0%	1.52 (0.91-2.53)	NS	5.1%	2.7%	1.9 (1.02-3.82)	< 0.05
TVR	19.6%	20.7%	0.98 (0.78-1.22)	NS	17.2%	19.8%	0.83 (0.64-1.06)	NS
MACE	26.3%	27.6%	0.99 (0.81-1.21)	NS	23.6%	24.9%	0.95 (0.76-1.18)	NS

CI = confidence interval; MACE = major adverse cardiac events (death, reinfarction, and/or TVR); MI = myocardial infarction; RR = relative risk; SAT = subacute thrombosis; TVR = target vessel revascularization.

limited percentage of patients. In fact, when taking into account all patients with STEMI during the same period, but not included in the trial, direct stenting was feasible in 53% (216/409) of total primary stenting procedures.

The reduction in fluoroscopic and procedural time and the feasibility of a direct stenting strategy in primary angioplasty have been confirmed by the DIRAMI trial[29], in which a total of 248 patients with STEMI were randomized to direct stenting or provisional stenting.

Drug-eluting stents in primary angioplasty. Restenosis still represents the Achille's heel of coronary angioplasty. Thus, the possibility of "a local solution for a local problem" represents a very attractive option. Although the benefits of drug-eluting stents on TVR have been shown in elective cases[30,31], and the initial results showed the feasibility of drug-eluting stents for STEMI[32], its safety issue in STEMI remains to be established by large randomized trials. In fact, the delayed re-endothelialization of drug-eluting stents may potentially be associated with higher rates of subacute thrombosis, with impairment of clinical outcome. Data from the Rotterdam registry[32], comparing 186 consecutive patients treated with sirolimus-eluting stent vs 183 patients treated with bare metal stents for STEMI, showed a significant reduction in TVR at 1-year follow-up (1.1 vs 8.2%), without higher risk of subacute stent thrombosis. Future randomized studies, without strict inclusion criteria, should be conducted to provide the safety and a cost-benefit analysis of an unrestricted use of drug-eluting stents in this high-risk subset of patients.

Abciximab in primary angioplasty

Rationale for glycoprotein IIb/IIIa inhibitors in primary angioplasty. The aim of a reperfusion therapy is to restore both epicardial (macrocirculation) and myocardial (microcirculation) flow. The strategy of incorporating IIb/IIIa inhibitors in primary angioplasty, aiming at a more effective initial reperfusion and a better sustained antithrombotic *milieu*, seems very attractive, particularly in association with stenting. In fact, the PAMI trial reported a paradoxical higher mortality in stenting patients, attributed to an observed impaired flow, in comparison with balloon angioplasty[11]. Among the different molecules currently used, only abciximab has been extensively tested in patients with STEMI[4,16,33-38].

Results of randomized trials. Several randomized trials have been conducted in primary angioplasty. However, the benefits from adjunctive abciximab have not been uniform across the studies. Several factors may explain for these data. In the two largest trials[4,16], patients in cardiogenic shock were excluded. This accounts for the lower risk population object of these two studies, confirmed by the low 6-month mortality rate observed in the control group of the RAPPORT (4.5%) and the CADILLAC (3.7%) trials.

Given the advances in primary angioplasty of the last decades[39], further attempts to reduce mortality are not easily demonstrated. Highly selected non-high-risk patients are commonly enrolled in randomized trials, whereas benefits on mortality have only been shown in trials enrolling high-risk patients[34-38]. Several non-randomized studies have shown significantly better survival in patients with cardiogenic shock treated with primary angioplasty and abciximab[40,41]. Therefore, future trials should be focused on high-risk patients, in whom reperfusion therapies still confer unsatisfactory results.

Furthermore, in the CADILLAC trial[16], a late randomization strategy let patients receive abciximab only after angiography. The potential benefits of early abciximab administration are demonstrated by the statistical significant difference in preprocedural recanalization between the abciximab and placebo group observed in the ADMIRAL trial[35] and the trial of Zorman et al.[38].

A recent meta-analysis has evaluated the benefits of abciximab as adjunctive to mechanical revascularization for STEMI in 8 randomized trials[42]. Among a total of 3949 patients, 2016 (51%) were randomized to abciximab. This study has shown that adjunctive abciximab was associated with a significant reduction in the 30-day reinfarction (1.0 vs 1.9%, OR 0.56, 95% CI 0.33-0.94, p = 0.03), mortality at 30-day (2.4 vs 3.4%, OR 0.68, 95% CI 0.47-0.99, p = 0.047), and 6-12-month (4.4 vs 6.2%, OR 0.69, 95% CI 0.52-0.92, p = 0.01) follow-up (Fig. 2), without any increase in the risk of intracranial (0.06 vs 0.11%, OR 0.97, 95% CI 0.31-3.01, p = 0.96) and major bleeding complications (4.7 vs 4.1%, OR 1.16, 95% CI 0.85-1.59, p = 0.36).

The benefits of abciximab in patients treated with primary angioplasty may be related to the fact that abciximab may prevent distal embolization and improve myocardial perfusion. As reported by the Zwolle group[43], distal embolization is observed in up to 16% of patients undergoing primary angioplasty, resulting in impaired myocardial perfusion and high long-term mortality. Furthermore, the reduction in early reinfarction after abciximab may further explain the benefits in mortality observed in angioplasty trials, particularly in those enrolling patients with cardiogenic shock.

Remaining questions to be addressed.

1) *Diabetes.* Still unclear is the impact of abciximab on mortality in diabetic patients undergoing primary angioplasty. Attention should be focused on this high-risk population, because of the benefits in mortality shown

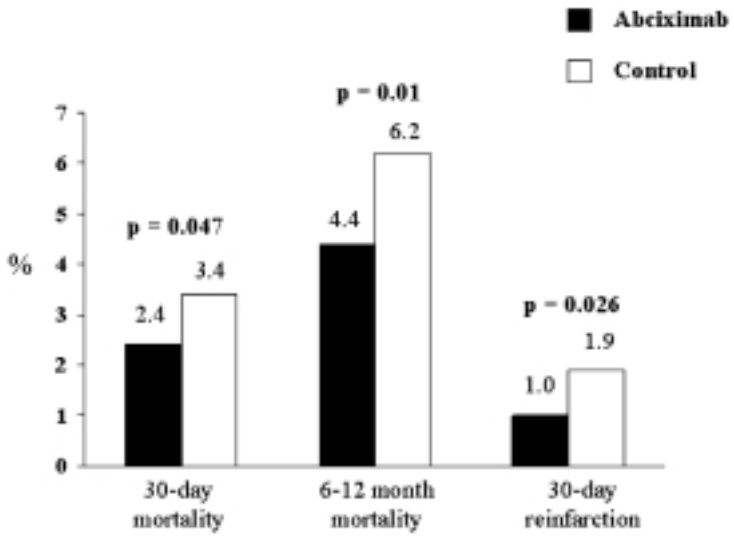

Figure 2. *Bar graphs show a pooled data analysis of the 30-day and 6-12-month clinical outcome from randomized trials on adjunctive abciximab to mechanical revascularization for ST-elevation myocardial infarction. Abciximab was associated with significant benefits in terms of death and reinfarction.*

by trials in diabetic patients undergoing elective angioplasty[44]. Data from the ADMIRAL trial[35] showed a significant reduction in mortality in these patients (0 vs 16.7%). No data have been reported from other trials[4,16,34,36-38].

2) *Timing of drug administration.* It is still unclear whether an early drug administration (at the time of diagnosis of STEMI) is more beneficial in comparison with late administration (after angiography). Only in the ADMIRAL[35] and the study of Zorman et al.[38] patients received abciximab in the intensive care unit or during transportation, with clear benefits in preprocedural angiographic flow and outcome. A recent meta-analysis of 6 randomized trials comparing early vs late IIb/IIIa inhibitor administration in primary angioplasty[45], 3 trials with abciximab[38,46,47] and 3 trials with tirofiban[48-50], showed significantly better preprocedural TIMI flow with early administration.

3) *Dosage.* Batchelor et al.[51] found a decreased intensity of platelet inhibition from 4 to 12 hours during abciximab infusion, in comparison with tirofiban and eptifibatide. One explanation may relate to the pharmacological aspects of abciximab. In fact, the lower concentration of unbound abciximab may be inadequate to inhibit the release of stored glycoprotein IIb/IIIa receptors during further platelet activation[52].

4) *Route of administration.* Recent reports (an observational study and a small randomized trial)[53,54] have shown that intracoronary administration of abciximab is superior to intravenous administration. These data may be explained by the fact that the high concentration obtained *in loco*[53] and distally to the occlusion[54] may better protect microcirculation from distal embolization and preserve its function. Future large randomized trials are certainly needed to further evaluate the potential benefits of intracoronary administration of IIb/IIIa inhibitors.

5) *Abciximab or small molecules in primary angioplasty?* The safety and benefits of transferring patients for primary angioplasty[55] make the strategy of incorporating early IIb/IIIa inhibitors and half-dose thrombolytic administration during transportation an attractive alternative ("facilitated angioplasty")[56]. This strategy may be associated with an early preprocedural recanalization, and may compensate any delay related to transportation to tertiary centers. Furthermore, the pharmacodynamic properties of small molecules (tirofiban and eptifibatide) may be more suitable for this strategy, as the costs and potential bleeding complications in case of urgent surgery, may be reduced.

Conclusions

As compared to balloon angioplasty, coronary stenting does not reduce mortality and reinfarction, despite the reduction in TVR. Furthermore, these benefits seem to be reduced when applied to unselected patients with STEMI. Direct stenting represents an attractive strategy with potential benefits in terms of myocardial perfusion. Future randomized trials are needed to evaluate if this strategy is associated with a significant impact on outcome, and to provide a cost-benefit analysis of an unrestricted use of drug-eluting stent in this high-risk subset of patients.

Abciximab seems to reduce mortality in primary angioplasty. Since the feasibility of long-distance transportation has been shown in several randomized trials, early pharmacological pretreatment may confer further advantages by early recanalization and shorter ischemic time, particularly in high-risk patients[57-59]. Further large randomized trials are needed to clarify the potential role of small molecules in primary angioplasty for STEMI.

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